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Congenital diaphragmatic hernia: Where and what is the evidence?

Paul D. Losty, MD, FRCSI, FRCS(Ed), FRCS(Eng), FRCS(Paed), FEBPS

Department of Paediatric Surgery, Alder Hey Children's Hospital NHS Foundation Trust, University of Liverpool, Liverpool, UK

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ABSTRACT

Congenital diaphragmatic hernia (CDH) retains high mortality and morbidity due to lung hypoplasia, pulmonary hypertension and severe co-existent anomalies. This article offers a comprehensive state-of-the-art review for the paediatric surgeon whilst also describing key contributions from the basic sciences in the search to uncover the cause of the birth defect together with efforts to develop new and better therapies for CDH.

Introduction

A few years ago, paediatric surgeons, neonatologists, foetal medicine specialists, genetic experts, scientists and CDH parent support organisations from many countries attended an international conference in Rome, Italy. Delegates witnessed an excellent two-and-half day meeting held at the congress venue in the nearby vicinity of the *Spanish Steps*. The objectives of the conference were clear for all invited guest speakers and key participants: "To review current progress whilst crucially addressing the evidence base of varied management strategies including the latest 'breaking news' together with advances in the field." This article is based (in part) on the invited lecture delivered by the author. Relevant work published since the Rome meeting is also included to provide the reader with a state-of-the-art 2014 update.

CDH is a lethal birth defect (1 in 3000 live births), which can be highly unpredictable. Paediatric surgeons working in clinical practice for many years will have witnessed, e.g., "small-for-date" or premature CDH babies survive (why?), whilst those considered "healthy term" low-risk newborns with CDH die from respiratory distress or pulmonary hypertension as a result of inadequate lung development. CDH is therefore an enigmatic condition and unsolved problem.[1] Advances leading to modest improvement(s) in survival have evolved from timely in utero diagnosis, newborn delivery at "high-volume" centres co-ordinated by multidisciplinary teams, along with the wider deployment in institutions worldwide of permissive hypercapnea strategies/"gentle ventilation" to avert fatal pulmonary barotrauma.[1] National and international CDH registries provide vital repositories for the paediatric surgical community with decisive publications helping benchmark a hospital or unit's team performance alongside providing contemporary data that may be used to determine practice variation, e.g., prenatal CDH risk categorisation, accurate case selection and recruitment (if appropriate) for foetal intervention in clinical trials and ongoing audit of hospital mortality/morbidity metrics including examining rate(s) of patch failure, revisional surgery and deciding which patients are perhaps best suited for minimally invasive operative repair.[1,2]

The foetus with CDH

Accurate prenatal diagnosis of CDH is now possible in many centres worldwide with detection rates steadily approaching 80%.[1] All cases should be referred to a specialist unit for full risk assessment. Prenatal diagnosis affords the opportunity for counselling by an experienced MDT team, which must include a paediatric surgeon, neonatologist, midwife and obstetrician. Delivery (if parents opt for continuation of pregnancy) is scheduled with induction of labour and vaginal delivery as near term as possible ideally at 38 weeks to avoid spontaneous onset of labour, which may prove hazardous for the CDH baby if birth occurs at a remote community hospital. Studies from Canada and Scandinavia strongly support the concept of management at high-volume centres (treating more than 5–6 CDH cases/year) with survival at such institutions notably better.[3,4] Prenatal detection raises the debate of foetal risk assessment, survival and outcome(s). Detailed

E-mail address: paul.losty@liverpool.ac.uk

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sonography and echocardiography with or without foetal MRI aim to exclude associated abnormalities most notably congenital heart disease and chromosomal anomalies. Expectant mothers should be offered amniocentesis with karyotyping. In foetal centres, imaging should record the laterality of the CDH defect, presence or absence of liver herniation ("liver up"), stomach in the chest and a true estimate of the observed:expected lung head ratio (O/E LHR). In a robust systematic review and meta-analysis published in 2010 by the CDH research group in Liverpool, we convincingly showed that liver herniation correlated with poor prognosis ("liver up" 45%—survival vs "liver down"—74%—better outcomes $P < 0.005$).[5] We further recommended grading the degree of liver herniation to refine outcomes further.[5] The absolute measurement of the lung: head ratio (LHR) was first introduced as a new prenatal marker in 1996 by Harrison's group at UCSF.[6] LHR was shown to be unreliable in a comprehensive study first presented at the BAPS International Congress meeting held in Stockholm, Sweden, in a research article delivered from Liverpool, later published in Ultrasound Obstetrics and Gynecology in 2007.[7] Inaccuracies in predicting survival in the CDH foetus with absolute LHR measurement(s) were readily explained by the near-total absence of normative data available for LHR on the developing foetus without CDH.[7]

To address the weaknesses of LHR, the observed:expected O/E LHR was developed by Jani et al.[8] taking into account key events associated with normal foetal growth as recommended by Liverpool researchers. The O/E LHR is now incorporated with a panel of other markers notably liver herniation as a prenatal scoring tool in selecting the "high-risk" foetus for intervention(s) before birth—see later. MRI lung volumetry may also be deployed to measure lung growth in the foetus. Along with the expanding potential (s) of imaging technologies to determine the status of the pulmonary vascular bed and the relationship to postnatal outcome(s) further large-scale evidence-based studies in the foetus with CDH are required.[9]

Foetal intervention and case selection

Excitement and great interest in foetal repair of CDH initially focused on the open operation of the diaphragmatic defect following maternal C-section hysterotomy. History and developments in foetal surgery are well described elsewhere.[10] Trials were discontinued due to preterm labour and poor foetal outcome. Jay Wilson at Boston Children's Hospital then published a decisive report showing that hypoplastic lungs in the surgically induced lamb model of diaphragmatic hernia could be accelerated to grow by occluding the foetal trachea.[11,12] Wilson et al's[11] key contribution to the field led to spectacular refinement in the experimental surgical approaches used to treat human CDH.[12] A decade later in 2003—Harrison et al.[13] in San Francisco (working on the idea (s) first pioneered by Wilson) reported the first randomised controlled trial of open hysterotomy-guided foetal endoscopic tracheal occlusion (FETO). The UCSF group showed equivalent survival 73% in the TO group vs 77% survival ($P = 1.00$) in "high-risk" foetuses also managed by conventional postnatal care (without TO).[13] The trial steering committee halted the trial. Twelve years later—largely led by efforts of European foetal medicine specialists, a new minimally invasive operation termed percutaneous foetal endoluminal tracheal occlusion (FETO) is being subjected to a new randomised clinical trial.[14,15] Selective entry criteria for the "high-risk" isolated CDH fetus now require an O/E LHR less than 27–28% with liver herniation (termed "liver up") being incorporated with trial entry. At the time of writing FETO is a much debated experimental procedure. It is recommended by the author that referral to UK, European, and North and South American centres should only be offered within the strictest ethical guidelines of a randomised controlled trial. In Liverpool, we provide ongoing care for CDH babies that have undergone the FETO procedure. The popular press, television media, internet, and CDH parent support organisations often widely advertise these high-profile cases. It is important and indeed morally correct that whilst having a duty to publicise latest innovations in health care, social media forums must also provide full and honest transparent information to expectant families. The FETO trial led by Deprest[15] and participating international centres will be published shortly.

Delivery and postnatal management

Delivery at a specialist centre is paramount to good out come(s).[1,3,4] Induction of labour and vaginal delivery should be planned as close to term as possible—38 weeks to allow adequate pulmonary maturation. In ideal circumstances, "inborn" delivery should take place at a single-centre site fully equipped to resuscitate the newborn. Elective intubation and "gentle ventilation" to avoid barotrauma is aimed at stabilising labile physiology whilst awaiting delayed operative repair. There are no indications for urgent surgical operation of the diaphragmatic defect and the index case should be scheduled as a day time not "out-of-hours" operation.[1] With the increasing antenatal detection rate of CDH, expert opinion regarding the best mode of delivery has been the subject of debate. In 2007, the CDH study group reported a marginal (nonsignificant) survival benefit for elective delivery by caesarean section.[16] Further randomised studies are needed to draw any definitive conclusions. All babies should have a nasogastric tube promptly inserted to avoid gastric distension and timely vascular access secured to aid delivery of fluids and pharmacological agents including inotropes. Following early stabilisation, a full clinical examination is required to exclude associated anomalies. Chest radiograph confirming the diagnosis and echocardiogram is performed to screen for cardiac anomalies.

Postnatal diagnosis—"Late presenting CDH"

Despite antenatal imaging, some 20–30% of patients with CDH may remain undetected until after delivery. Such cases may present in the immediate newborn period or first few days after birth whilst others may remain asymptomatic until later life. Symptoms here may include mild respiratory distress or feeding problems. Delayed presentation may occur with small diaphragmatic defects in which there is little or no herniated bowel at birth. These infants are at a potential risk for gut infarction from incarcerating thoracic viscera through a small diaphragm defect.[1] Clinical examination may reveal bowel sounds on chest auscultation. There may be signs of decreased air entry on the affected side and rarely mediastinal shift. Diagnosis is often made on a chest radiograph but may require an upper gastrointestinal contrast study for further confirmation.

Stabilisation

"Gentle" ventilation has been one of the leading major advances in the management of CDH. It was designed (permissive hypercapnea) to reduce iatrogenic lung injury from barotrauma. Wung et al.[17] introduced this novel concept characterised by preservation of spontaneous ventilation, permissive levels of hypercapnea and avoidance of high inspiratory airway pressures (ideally not exceeding 25 cmH_2O). A number of centres, including Liverpool, have steadily reported improving outcomes (more than 80% survival) by adopting this approach together with a much reduced need for ECMO.[1,18] High-frequency oscillatory ventilation (HFOV) has been